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NEWS 31 Apr 14 MEDLINE Reload  
NEWS 32 Apr 17 Polymer searching in REGISTRY enhanced  
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added to PHAR  
NEWS 37 May 15 MEDLINE file segment of TOXCENTER reloaded  
NEWS 38 May 15 Supporter information for ENCOMPAT and ENCOMPLIT  
updated  
NEWS 39 May 16 CHEMREACT will be removed from STN  
NEWS 40 May 19 Simultaneous left and right truncation added to WSCA  
NEWS 41 May 19 RAPRA enhanced with new search field, simultaneous left and  
right truncation  
NEWS 42 Jun 06 Simultaneous left and right truncation added to CBNB  
NEWS 43 Jun 06 PASCAL enhanced with additional data  
NEWS 44 Jun 20 2003 edition of the FSTA Thesaurus is now available  
NEWS 45 Jun 25 HSDB has been reloaded

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CURRENT

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L1 481 VP16 (3A) FUSI?

=> s I1 and tet  
L2 47 L1 AND TET

=> s I2 and transgen? -  
L3 22 L2 AND TRANSGEN?

=> dup rem I3  
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L4 20 DUP REM L3 (2 DUPLICATES REMOVED)

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L4 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 2003:236446 CAPLUS  
DN 139:1619  
TI Reengineering Inducible Cardiac-Specific \*\*\*Transgenesis\*\*\* With an  
Attenuated Myosin Heavy Chain Promoter  
AU Sanbe, Atsushi; Gulick, James; Hanks, Mark C.; Liang, Qiangrong; Osinska,  
Hanna; Robbins, Jeffrey  
CS Dep. Pediatr., Div. Mol. Cardiovasc. Biol., Child. Hosp. Res. Found.,  
Cincinnati, OH, USA  
SO Circulation Research (2003), 92(6), 609-616  
CODEN: CIRUAL; ISSN: 0009-7330  
PB Lippincott Williams & Wilkins  
DT Journal  
LA English  
AB Despite the advantages of reversibly altering cardiac \*\*\*transgene\*\*\*  
expression, the no. of successful studies with inducible cardiac-specific  
\*\*\*transgene\*\*\* expression remains limited. The utility of the current  
system is hampered by the large no. of lines needed before a nonleaky  
inducible line is isolated and by the use of a heterologous virus-based  
minimal promoter in the responder line. We developed an efficient, extpl.  
flexible system that enables us to reversibly affect both abundant and  
nonabundant cardiomyocyte proteins. The use of bacterial-codon-based  
transactivators led to aberrant splicing, whereas other more efficient  
transactivators, by themselves, caused disease when expressed in the  
heart. The redesign of the system focused on developing stable  
transactivator-expressing lines in which expression was driven by the  
mouse .alpha.-myosin heavy chain promoter. A minimal responder locus was  
derived from the same promoter, in which the GATA sites and thyroid  
responsive elements responsible for robust cardiac specific expression  
were ablated, leading to an attenuated promoter that could be inducibly  
controlled. In all cases, whether activated or not, expression mimicked  
that of the parental promoter. By use of this system, an inducible  
expression of an abundant contractile protein, the atrial isoform of  
essential myosin light chain 1, and a powerful biol. effector, glycogen  
synthase kinase-3.beta. (GSK-3.beta.), were obtained. Subsequently, we  
tested the hypothesis that GSK-3.beta. expression could reverse a  
preexisting hypertrophy. Inducible expression of GSK-3.beta. could both  
attenuate a hypertrophic response and partially reverse a  
pressure-overload-induced hypertrophy. The system appears to be robust  
and can be used to temporally control high levels of cardiac-specific  
\*\*\*transgene\*\*\* expression.

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS  
RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 2002:836498 CAPLUS  
DN 138:199500  
TI A predictable ligand regulated expression strategy for stably integrated  
\*\*\*transgenes\*\*\* in mammalian cells in culture  
AU Anastassiadis, Konstantinos; Kim, Jinhyun; Daigle, Nathalie; Sprengel,  
Rolf; Scholer, Hans R.; Stewart, A. Francis  
CS Max-Planck-Institut für Molekulare Zellbiologie und Genetik MPI-CBG,  
BIOTEC, TU Dresden, Dresden, 01307, Germany  
SO Gene (2002), 298(2), 159-172  
CODEN: GENED6; ISSN: 0378-1119  
PB Elsevier Science B.V.  
DT Journal  
LA English  
AB Several strategies for regulated stable \*\*\*transgene\*\*\* expression in  
mammalian cells have been described. These strategies have different  
strengths and weaknesses, however they all share a common problem, namely  
predictability in application. Here we address this problem using the

leading strategy for ligand inducible \*\*\*transgene\*\*\* expression, the tetracycline repressor system. Initially, we found the best stable clone out of 48 examd. showed only 6-fold inducibility. Hence we looked for addns. and modifications that improve the chances of a successful outcome. We document three important aspects; first, use of a mammalian codon-optimized tetracycline repressor gene; second, addn. of a steroid hormone receptor ligand binding domain to the tetracycline repressor-virion protein 16 fusion protein activator; third, flanking the \*\*\*tet\*\*\* -operator/ \*\*\*transgene\*\*\* cassette with insulator elements from the chicken .beta.-globin locus. By inclusion of these three design features, 18/18 clones showed low basal and highly inducible (>50.times.) expression.

RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 2001:851354 CAPLUS

DN 135:370244

TI Over-expression of glycogen synthase kinase-3.beta. in a murine model for neurodegenerative disease

IN Perez, Felix Hernandez; De Grado, Jesus Avila

PA Consejo Superior de Investigaciones Cientificas, Spain; Ruffles, Graham Keith; Lozano, Jose Javier Lucas

SO PCT Int. Appl., 47 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

| PATENT NO.         | KIND  | DATE     | APPLICATION NO. | DATE     |
|--------------------|---|----------|-----------------|----------|
| PI WO 2001088109   | A2  | 20011122 | WO 2001-GB2218  | 20010518 |
| WO 2001088109      | A3  | 20020704 |                 |          |
| WO 2001088109      | C1  | 20020926 |                 |          |
| W:                 | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  |          |                 |          |
| RW:                | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GV, ML, MR, NE, SN, TD, TG  |          |                 |          |
| EP 1280404         | A2  | 20030205 | EP 2001-936609  | 20010518 |
| R:                 | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR  |          |                 |          |
| PRAI GB 2000-12056 | A   | 20000518 |                 |          |
| WO 2001-GB2218     | W   | 20010518 |                 |          |
| AB                 | A ***transgenic*** animal in which glycogen synthase kinase-3.beta. (GSK-3.beta.) protein is over-expressed is useful as a model for neurodegenerative disease. Regulation of the system is achieved through the tetracycline-regulated transactivator, a chimeric protein comprises of the ***tet*** -repressor DNA binding domain and the VP16 trans-activation domain. Conditional ***transgenic*** mice overexpressing GSK-3.beta. in the brain during adulthood is thus achieved, while avoiding perinatal lethality due to embryonic ***transgene*** expression. These mice show destabilization of .beta.-catenin and hyperphosphorylation of .tau. protein in hippocampus neurons, the latter resulting in pretangle-like somatodendritic localization of .tau.. Neurons displaying somatodendritic localization of .tau. often show abnormal morphologies and detachment from surrounding neuropil. Reactive astrocytosis and microgliosis were indicative of neuronal stress and death. Thus, in vivo overexpression of GSK-3.beta. results in neurodegeneration and these mice can be used as an animal model to study the relevance of GSK-3.beta. deregulation to the pathogenesis of Alzheimer's disease. |          |                 |          |

L4 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 2001:319911 CAPLUS

DN 134:321592

TI Methods to enhance and confine gene expression in cancer therapy

IN Fung, Yuen Kai; Tang, Anne

PA Research Development Foundation, USA

SO PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

| PATENT NO.           | KIND   | DATE     | APPLICATION NO. | DATE     |
|----------------------|--|----------|-----------------|----------|
| PI WO 2001030799     | A1   | 20010503 | WO 2000-US29783 | 20001027 |
| W:                   | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |          |                 |          |
| RW:                  | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GV, ML, MR, NE, SN, TD, TG   |          |                 |          |
| PRAI US 1999-162085P | P  | 19991028 |                 |          |
| AB                   | The present invention provides a novel approach to gene therapy of restricted areas such as tumors. More specifically the present invention  |          |                 |          |

presents a method of controlling the expression of therapeutically useful gene products via tissue specific, tumor specific, and inducible promoters to allow enhanced expression of these genes in tumor cells while reducing the background expression of these genes in nontarget cells. The methods introduced here comprise: (a) placing a gene of interest in a plasmid vector driven by a tissue specific promoter or a heat or light inducible promoter; and (b) modifying this vector by including a tetracycline responsive fusion protein which acts as a transcriptional activator, thus permitting regulation of gene expression by varying the levels of tetracycline; (c) modifying this vector by including DNA sequences that reduce or eliminate expression of genes in unintended cells. Also provided are a set of vectors for both sustained and regulated expression. There are also presented novel vectors for the gene therapy treatment of metastatic breast, ovarian and prostate cancer.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 2001:886858 CAPLUS

DN 136:1607

TI Use of a tetracycline-controlled promoter, activator and antisense gene in tissue-specific expression in \*\*\*transgenic\*\*\* mice

IN Orosz, Charles G.; Xia, Dongyuan; Gordillo, Gayle M.

PA USA

SO U.S. Pat. Appl. Publ., 26 pp.

CODEN: USXXCO

DT Patent

LA English

FAN.CNT 1

| PATENT NO.          | KIND   | DATE     | APPLICATION NO. | DATE     |
|---------------------|--|----------|-----------------|----------|
| PI US 2001049828    | A1   | 20011206 | US 2000-547489  | 20000412 |
| PRAI US 2000-547489 |  |          | 20000412        |          |
| AB                  | A method and system for controlling the expression of ***transgene*** products in specific tissues in a ***transgenic*** animal while eliminating background expression of the ***transgene*** products in tissues of the animal is provided. The system is a modified form of the tetracycline-regulated expression system for use in mice. The animals with low background expression of the gene are the offspring of a cross between parental mice carrying different components of the regulatory system. One of the parents carries a foreign gene under control of an inducible promoter. The promoter is induced by a transcription factor activated by ligand binding. The second animal carries two genes: one is an antisense version of the ***transgene*** carried by the other parent. This promoter is down-regulated or repressed by the transcription factor that induces the sense form of the gene. The second gene is the gene for the transcription factor under control of a tissue-specific promoter. In the offspring, low levels of leaky gene expression of the sense gene outside the target tissue are blocked by comparable levels of expression of the antisense gene. In the target tissue the expression of the antisense gene is repressed, allowing expression of the desired gene. In a preferred embodiment, the transactivator regulator is tetracycline and the transactivator protein is the rTA protein. Administration of a transactivator regulator like tetracycline to a mouse, produced in accordance with the method described above, results in enhanced expression of the exogenous gene and reduced expression of the antisense gene product in target tissues. Accordingly, the mouse can be used for studying the impact of the ***transgene*** product on the biol. of the mouse under defined conditions of expression. |          |                 |          |

L4 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 2001:471732 CAPLUS

DN 136:145744

TI \*\*\*Tet\*\*\* -system for the regulation of gene expression during embryonic development

AU Fedorov, Lev M.; Tyrsin, Oleg Yu.; Krenn, Veit; Chernigovskaya, Elena V.; Rapp, Ulf R.

CS Institut für Medizinische Strahlenkunde und Zellforschung, Bayerische Julius-Maximilians-Universität Würzburg, Würzburg, D-97078, Germany

SO Transgenic Research (2001), 10(3), 247-258

CODEN: TRSEES; ISSN: 0962-8819

PB Kluwer Academic Publishers

DT Journal

LA English

AB The ability to control gene expression in a temporal and spatial manner provides a new tool for the study of mammalian gene function particularly during development and oncogenesis. In this study the suitability of the \*\*\*tet\*\*\* -system for investigating embryogenesis was tested in detail. The tTACMV (M1) and rTACMV -3 (reverse Tc-controlled transactivator) \*\*\*transgenic\*\*\* mice were bred with NZL-2 bi-reporter mice contg. the vector with a tTA/tTA responsive bidirectional promoter that allows simultaneous regulation of expression of two reporter genes encoding luciferase and .beta.-galactosidase. In both cases reporter genes were found to be expressed in a wide spectrum of tissues of double \*\*\*transgenic\*\*\* embryos and adult mice. The earliest expression was detected in tTACMV (M1)/NZL-2 embryos at embryonic day 10.5 (E10.5) and rTACMV -3/NZL-2 embryos at E13.5. Doxycycline abolished .beta.-gal expression in tTACMV (M1)/NZL-2 but induced it in rTACMV -3/NZL-2 embryos including late stages of embryogenesis. The tTA and rTA transactivators thus revealed a partially complementary mode of action during second half of embryonic development. These expts. demonstrated that both \*\*\*Tet\*\*\* regulatory systems function during embryonic development. We conclude

that the \*\*\*Tet\*\*\* systems allows regulation of gene expression during embryonic development and that "double reporter" animals like the NZL-2 mice are useful tools for the characterization of newly generated \*\*\*tet\*\*\* transactivator lines expressing tTA (or rTA) in embryonic as well as in adult tissues.

RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 2001:909214 CAPLUS  
DN 136:364436

TI Modulation of myosin A expression by a newly established tetracycline repressor-based inducible system in *Toxoplasma gondii*

AU Meissner, Markus; Brecht, Susan; Bujard, Hermann; Soldati, Dominique  
CS Zentrum für Molekulare Biologie, Universität Heidelberg, Heidelberg, 69102, Germany

SO Nucleic Acids Research (2001), 29(22), e1151-e1151/0  
CODEN: NARHAD; ISSN: 0305-1048

PB Oxford University Press

DT Journal

LA English

AB We have developed a control system for regulating gene activation in *Toxoplasma gondii*. The elements of this system are derived from the *Escherichia coli* tetracycline resistance operon, which has been widely used to tightly control gene expression in eukaryotes. The tetracycline repressor (tetR) interferes with transcription initiation while the chimeric transactivator, composed of the tetR fused to the activating domain of VP16 transcriptional factor, allows \*\*\*tet\*\*\*-dependent transcription. Accordingly, tetracycline derivs. such as anhydrotetracycline, which is well tolerated by *T. gondii*, can serve as effector mol's., allowing control of gene expression in a reversible manner. As a prerequisite to functionally express the tetR in *T. gondii*, the authors used a synthetic gene with change of codon frequency. Whereas no activation of transcription was achieved using the synthetic tetracycline-controlled transactivator, tTA2s, the TetRs modulates parasite transcription over a range of approx. 15-fold as measured for several reporter genes. The tetR-dependent induction of the *T. gondii* myosin A \*\*\*transgene\*\*\* expression drastically down-regulates the level of endogenous MyoA. This myosin is under the control of a tight feedback mechanism, which occurs at the protein level.

RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 2002:520955 CAPLUS  
DN 138:67414

TI A regulatory network for the efficient control of \*\*\*transgene\*\*\* expression

AU Imhof, Markus O.; Chatellard, Philippe; Mermoud, Nicolas  
CS Laboratory of Molecular Biotechnology, Center for Biotechnology UNIL-EPFL, University of Lausanne, Lausanne, 1015, Switz.

SO Journal of Gene Medicine (2000), 2(2), 107-116

CODEN: JGMEFG; ISSN: 1099-498X

PB John Wiley & Sons Ltd.

DT Journal

LA English

AB Expression of heterologous genes in mammalian cells or organisms for therapeutic or exptl. purposes often requires tight control of \*\*\*transgene\*\*\* expression. Specifically, the following criteria should be met: no background gene activity in the off-state, high gene expression in the on-state, regulated expression over an extended period, and multiple switching between on- and off-states. Here, the authors describe a genetic switch system for controlled \*\*\*transgene\*\*\* transcription using chimeric repressor and activator proteins functioning in a novel regulatory network. In the off-state, the target \*\*\*transgene\*\*\* is actively silenced by a chimeric protein consisting of multimerized eukaryotic transcriptional repression domains fused to the DNA-binding tetracycline repressor. In the on-state, the inducer drug doxycycline affects both the derepression of the target gene promoter and activation by the GAL4-VP16 transactivator, which in turn is under the control of an autoregulatory feedback loop. The hallmark of this new system is the efficient \*\*\*transgene\*\*\* silencing in the off-state, as demonstrated by the tightly controlled expression of the highly cytotoxic diphtheria toxin A gene. Addn. of the inducer drug allows robust activation of \*\*\*transgene\*\*\* expression. In stably transfected cells, this control is still obsd. after months of repeated cycling between the repressed and activated states of the target genes. This system permits tight long-term regulation when stably introduced into cell lines. The underlying principles of this network system should have general applications in biotechnol. and gene therapy.

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 1999:64930 CAPLUS  
DN 130:120493

TI A nuclear receptor from *Bombyx* that act as a transcriptional regulator and its use in the expression of \*\*\*transgenes\*\*\* in animal cells

IN Gage, Fred H.; Suhr, Steven T.

PA The Salk Institute for Biological Studies, USA

SO PCT Int. Appl., 143 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|------|-----------------|------|
|------------|------|------|-----------------|------|

|               |  |          |                 |          |
|---------------|--|----------|-----------------|----------|
| PI WO 9902683 | A1   | 19990121 | WO 1998-US14215 | 19980710 |
| W:            | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |          |                 |          |
| RW:           | GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG   |          |                 |          |
| US 6300488    | B1   | 20011009 | US 1997-891298  | 19970710 |
| AU 9883895    | A1   | 19990208 | AU 1998-83895   | 19980710 |
| AU 738494     | B2   | 20010920 |                 |          |
| EP 998560     | A1   | 20000510 | EP 1998-934353  | 19980710 |
| R:            | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI   |          |                 |          |

|               |    |          |                |          |
|---------------|----|----------|----------------|----------|
| US 2002048815 | A1 | 20020425 | US 2001-952559 | 20010913 |
|---------------|----|----------|----------------|----------|

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| PRAI US 1997-891298 | A2 | 19970710 |  |  |
|---------------------|----|----------|--|--|

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|----------------|---|----------|--|--|
| US 1998-91874P | P | 19980707 |  |  |
|----------------|---|----------|--|--|

|                 |   |          |  |  |
|-----------------|---|----------|--|--|
| WO 1998-US14215 | W | 19980710 |  |  |
|-----------------|---|----------|--|--|

AB A nuclear receptor (bR) of the silk moth *Bombyx mori* that is useful for the regulation of expression of foreign genes in insect cells is described. BR is thought to be a strong transcriptional regulator in cells of *B. mori* and it is found to be functional in mammalian cells. Addn. of activation domains to the bR open-reading frame increases the activity of the ligand modulated regulator to afford high-level transcriptional induction. Further modifications to the bR ligand binding domain result in receptors with unique transactivation characteristics. A major advantage of the use of bR is that its natural ligand is not manufd. by mammalian cells, such as diacyl hydrazines, allowing strict control of gene expression using relatively small proteins. A particular example of this is a fusion protein of the receptor, the activation domain of VP16 and the \*\*\*tet\*\*\* repressor called TTMT (Tebufenozide/Tetracycline Modulated Transactivator) that uses the tetO operator and the ecdysone response element to regulate gene expression by repression (with tetracyclines) and activation by acylhydrazines. Regulation of expression of a reporter gene from a TTMT-responsive promoter by tebufenozide and muristerone A is demonstrated.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 1999:48795 CAPLUS  
DN 130:108060

TI \*\*\*VP16\*\*\* proteins carrying substitutions in repeats of the the transcription activation domain with different and defined transactivation potentials

IN Baron, Udo; Gossen, Manfred; Bujard, Hermann

PA BASF Aktiengesellschaft, USA

SO PCT Int. Appl., 56 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|------|-----------------|------|
|------------|------|------|-----------------|------|

|                     |  |          |                 |          |
|---------------------|--|----------|-----------------|----------|
| PI WO 9901549       | A1   | 19990114 | WO 1998-US13993 | 19980701 |
| W:                  | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |          |                 |          |
| RW:                 | GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG   |          |                 |          |
| US 6087166          | A  | 20000711 | US 1997-888080  | 19970703 |
| AU 9881825          | A1   | 19990125 | AU 1998-81825   | 19980701 |
| AU 755417           | B2   | 20021212 |                 |          |
| EP 990030           | A1   | 20000405 | EP 1998-931801  | 19980701 |
| R:                  | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO   |          |                 |          |
| JP 2002507895       | T2   | 20020312 | JP 1999-507457  | 19980701 |
| US 6271341          | B1   | 20010807 | US 2000-577027  | 20000523 |
| US 2003049842       | A1   | 20030313 | US 2001-922568  | 20010803 |
| PRAI US 1997-888080 | A2   | 19970703 |                 |          |
| WO 1998-US13993     | W  | 19980701 |                 |          |
| US 2000-577027      | A3   | 20000523 |                 |          |

AB Transcription activating proteins which differ in their transcription activation potential by more than 3 orders of magnitude are described. The transactivators are fusions of a DNA binding protein (e.g., the \*\*\*Tet\*\*\* repressor tetR) and minimal transcriptional activation domains derived from Herpes simplex virus protein 16 (VP16). Substitution mutations at amino acid position 442 within the minimal VP16 domain provide transactivators with differing transactivation ability. Chimeric activation domains contg. wild type and mutant minimal VP16 domains provide addnl. variants with differing transactivation ability. Various

aspects of the invention pertain to nucleic acid mols., vectors, host cells, fusion proteins, \*\*\*transgenic\*\*\* and homologous recombinant organisms and methods of regulating gene transcription. A series of fusion proteins of tetR and VP16 transcription activation domain analogs were constructed and tested for their ability to drive expression of a reporter gene in response to tetracyclines. Fusion proteins contg. an inactive analog of the activation peptide showed low levels of induction by tetracycline (gtoreq 0.03% of a tetR- \*\*\*VP16\*\*\* \*\*\*fusion\*\*\* protein control). Fusion proteins contg. an active analog of the activation peptide showed levels of induction up 230% of controls.  
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2003 ACS

AN 1999:808649 CAPLUS

DN 132:45794

TI Methods for regulation of gene expression using tetO-linked genes controlled by tetR or tetR mutant fusion proteins

IN Bujard, Hermann; Gossen, Manfred

PA BASF A.-G., Germany; Basf Bioresearch Corp.; Knoll A.-G.

SO U.S., 64 pp., Cont.-in-part of U.S. 5,789,156.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 12

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| PI US 6004941 | A | 19991221 | US 1995-485740 | 19950607 |
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| US 5464758 | A | 19951107 | US 1993-76726 | 19930614 |
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| US 5650298 | A | 19970722 | US 1994-260452 | 19940814 |
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| US 5654168 | A | 19970805 | US 1994-275876 | 19940715 |
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| US 5789156 | A | 19980804 | US 1995-383754 | 19950203 |
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| PRAI US 1993-76327 | B2 | 19930614 |  |  |
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| US 1993-76726 | A2 | 19930614 |  |  |
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| US 1994-260452 | A2 | 19940614 |  |  |
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| US 1994-270637 | B2 | 19940701 |  |  |
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| US 1994-275876 | A2 | 19940715 |  |  |
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| US 1995-383754 | A2 | 19950203 |  |  |
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AB Nucleic acid mols. and proteins useful for regulating the expression of genes in eukaryotic cells and organisms are disclosed. The invention provides a transcriptional activator fusion protein which binds to \*\*\*tet\*\*\* operator sequences and stimulates transcription of a \*\*\*tet\*\*\* operator-linked gene in the presence, but not the absence, of tetracycline (or analog thereof). The invention further provides transcriptional inhibitor fusion proteins which inhibit transcription of a \*\*\*tet\*\*\* operator-linked gene in a regulated manner. In one embodiment, the inhibitor fusion protein binds to \*\*\*tet\*\*\* operator sequences in the absence, but not the presence, of tetracycline (or analog). In another embodiment, the inhibitor fusion protein binds to \*\*\*tet\*\*\* operator sequences in the presence, but not the absence, of tetracycline (or analog). The transcriptional activator and inhibitor fusion proteins of the invention can be used in combination to regulate expression of one or multiple \*\*\*tet\*\*\* operator-linked genes. Novel \*\*\*tet\*\*\* operator-contg. transcription units which allow for coordinate or independent tetracycline-regulated expression of two or more genes by the transcriptional modulators of the invention are also disclosed. A gene for a \*\*\*tet\*\*\* repressor which binds to its target DNA in the presence rather than the absence of tetracycline was prep. by mutagenesis. This gene was fused to a sequence encoding the C-terminal 130 amino acids of herpes simplex virus VP16 to create a chimeric gene encoding a tetracycline-inducible transactivator. This transactivator was shown to function in HeLa cells and in \*\*\*transgenic\*\*\* mice. Activation by 3-5 orders of magnitude was obsd. upon addn. of tetracycline (or tetracycline analog). Genes for tetracycline-regulated transcriptional inhibitors comprising TetR fused to a v-erbA or Krueppel silencer domain were also prep. In addn., a combinatorial anal. of amino acid-substituted analogs of the TetR repressor and base-substituted analogs. of the operator was undertaken to find combinations showing the most effective induction or repression.

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2003 ACS

AN 1999:392567 CAPLUS

DN 131:40552

TI Mice \*\*\*transgenic\*\*\* for a tetracycline-inducible transcriptional activator

IN Bujard, Hermann; Gossen, Manfred

PA University of Heidelberg, Germany

SO U.S., 63 pp., Cont.-in-part of U.S. Ser. No. 383,754.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 12

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| PI US 5912411 | A | 19990615 | US 1995-487472 | 19950607 |
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| US 5464758 | A | 19951107 | US 1993-76726 | 19930614 |
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| US 5650298 | A | 19970722 | US 1994-260452 | 19940814 |
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| US 5654168 | A | 19970805 | US 1994-275876 | 19940715 |
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| US 5789156 | A | 19980804 | US 1995-383754 | 19950203 |
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US 6242667 B1 20010605 US 1998-161902 19980928

PRAI US 1993-76327 B2 19930614

US 1993-76726 A2 19930614

US 1994-260452 A2 19940614

US 1994-270637 B2 19940701

US 1994-275876 A2 19940715

US 1995-383754 A2 19950203

US 1995-487472 A1 19950607

AB Nucleic acid mols. and proteins useful for regulating the expression of genes in eukaryotic cells and organisms are disclosed. The invention provides a transcriptional activator fusion protein which binds to \*\*\*tet\*\*\* operator sequences and stimulates transcription of a \*\*\*tet\*\*\* operator-linked gene in the presence, but not the absence, of tetracycline (or analog thereof). The invention further provides transcriptional inhibitor fusion proteins which inhibit transcription of a \*\*\*tet\*\*\* operator-linked gene in a regulated manner. In one embodiment, the inhibitor fusion protein binds to \*\*\*tet\*\*\* operator sequences in the absence, but not the presence, of tetracycline (or analog). In another embodiment, the inhibitor fusion protein binds to \*\*\*tet\*\*\* operator sequences in the presence, but not the absence, of tetracycline (or analog). The transcriptional activator and inhibitor fusion proteins of the invention can be used in combination to regulate expression of one or multiple \*\*\*tet\*\*\* operator-linked genes. Novel \*\*\*tet\*\*\* operator-contg. transcription units which allow for coordinate or independent tetracycline-regulated expression of two or more genes by the transcriptional modulators of the invention are also disclosed. A gene for a \*\*\*tet\*\*\* repressor which binds to its target DNA in the presence rather than the absence of tetracycline was prep. by mutagenesis. This gene was fused to a sequence encoding the C-terminal 130 amino acids of herpes simplex virus VP16 to create a chimeric gene encoding a tetracycline-inducible transactivator. This transactivator was shown to function in HeLa cells and in \*\*\*transgenic\*\*\* mice. Activation by 3-5 orders of magnitude was obsd. upon addn. of tetracycline (or tetracycline analog). Genes for tetracycline-regulated transcriptional inhibitors comprising TetR fused to a v-erbA or Krueppel silencer domain were also prep. In addn., a combinatorial anal. of amino acid-substituted analogs of the TetR repressor and base-substituted analogs. of the operator was undertaken to find combinations showing the most effective induction or repression.

RE.CNT 91 THERE ARE 91 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2003 ACS

AN 1998:344524 CAPLUS

DN 129:13217

TI Diminishing viral gene expression by promoter replacement in adenoviral vectors

IN Fang, Bingliang; Roth, Jack A.

PA Board of Regents, The University of Texas System, USA; Fang, Bingliang; Roth, Jack A.

SO PCT Int. Appl., 118 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| PI WO 9821350 | A1 | 19980522 | WO 1997-US20608 | 19971112 |
|---------------|----|----------|-----------------|----------|

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, BG, KZ, MD, RU, TJ, TM  
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

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| AU 9852539 | A1 | 19980603 | AU 1998-52539 | 19971112 |
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| US 6110744 | A | 20000829 | US 1997-968014 | 19971112 |
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PRAI US 1998-30875P P 19981113

WO 1997-US20608 W 19971112

AB The present invention provides viral vectors that have been engineered to contain a synthetic promoter that controls at least one essential gene. The synthetic promoter is induced by a specific gene product not normally produced in the cells in which the viral vector is to be transferred. The vectors are propagated in producer or helper cells that express the inducing factor, thereby permitting the virus to replicate to high titer. The lack of the inducing factor in the target cells precludes viral replication, however, meaning that no vector toxicity or immunogenicity arises. Where the virus carries a gene of interest, this should provide for higher level expression for longer periods of time than with current vectors. Methods for making the vectors, helper cells, and their use in protein prodn., vaccines and gene therapy are disclosed. Thus, the promoter region of adenovirus E4 was replaced with a synthetic promoter composed of a minimal TATA box and five consensus 17-mer GAL4-binding site elements (GAL4/TATA). A shuttle vector consisting of the adenovirus type 5 backbone into which a human factor IX \*\*\*transgene\*\*\* driven by the Rous sarcoma virus-LTR was inserted into the E1 region was used to supply the adenoviral E4 region. Recombinant adenoviruses contg. the RSV promoter-derived human factor IX cDNA and adenovirus E4 gene driven by the GAL4/TATA promoter were constructed by cotransfection of the transfer plasmids with a fragment contg. human factor IX \*\*\*transgene\*\*\* into producer cells. The resulting recombinant adenoviruses obtained by

homologous recombination, when transduced into non-producer cells, maintain high levels of \*\*\*transgene\*\*\* expression while at the same time exhibit low levels of adenoviral gene expression. The recombinant adenoviruses exhibit reduced toxicity and attenuated CTL response resulting from E4 inactivation.

RE,CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 1997:465710 CAPLUS  
DN 127:171988

TI Tetracycline-controlled transcription in eukaryotes: novel transactivators with graded transactivation potential

AU Baron, Udo; Gossen, Manfred; Bujard, Hermann  
CS ZMBH, Heidelberg, 69120, Germany

SO Nucleic Acids Research (1997), 25(14), 2723-2729  
CODEN: NARHAD; ISSN: 0305-1048

PB Oxford University Press  
DT Journal

LA English

AB Several tetracycline-controlled transactivators (tTA) were generated which differ in their activation potential by >3 orders of magnitude. The transactivators are fusions between the \*\*\*Tet\*\*\* repressor and minimal transcriptional activation domains derived from Herpes simplex virus protein 16 (VP16). By reducing the VP16 moiety of the previously described tTA to 12 amino acids, potential targets for interactions with various cellular transcription factors were eliminated, as were potential epitopes which may elicit a cellular immune response. When compared with the originally described tTA, these new transactivators are tolerated at higher intracellular concns. This will facilitate establishment of \*\*\*tet\*\*\* regulatory systems under a variety of conditions, but particularly when cell type-restricted tetracycline-controlled gene expression is to be achieved in \*\*\*transgenic\*\*\* organisms via homologous recombination.

L4 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 1997:127494 CAPLUS  
DN 126:127877

TI An autoregulatory tetracycline-regulated system for inducible gene expression in eukaryotes

IN Schatz, David G.

PA Yale University, USA; Schatz, David G.

SO PCT Int. Appl., 81 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN,CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| PI  | WO 9640946 | A1 | 19961219 | WO 1996-US10109 | 19960607 |
| W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG |            |    |          |                 |          |

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| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA |  |  |  |  |  |
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| US 5851798 | A | 19981222 | US 1995-474169 | 19950607 |  |
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| AU 9662745 | A1 | 19961230 | AU 1996-62745 | 19960607 |  |
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| EP 832254 | A1 | 19980401 | EP 1996-921541 | 19960607 |  |
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| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI |  |  |  |  |  |
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| JP 11507539 | T2 | 19990706 | JP 1996-502206 | 19960607 |  |
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| PRAI US 1995-474169 | 19950607 |  |  |  |  |
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| WO 1996-US10109 | 19960607 |  |  |  |  |
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AB A tetracycline-regulated system which provides autoregulatory, inducible gene expression in cultured cells and \*\*\*transgenic\*\*\* animals is described. In the autoregulatory plasmid pTet-tTAk, a modified tTA gene called tTAk was placed under the control of Tetp. Tetracycline prevents tTA from binding to Tetp, preventing expression of both tTA and luciferase. This neg. feedback cycle ensures that little or no tTA is produced in the presence of tetracycline, thereby reducing or eliminating possible toxic effects. When tetracycline is removed, however, this strategy predicts that tiny amts. of tTA protein (which may result from the leakiness of the minimal promoter), will bind to \*\*\*Tet\*\*\* -op and stimulate expression of the tTAk gene. A pos. feedforward loop is initiated which in turn leads to higher levels of expression of tTA and thus, luciferase. Polynucleotide moles. encoding the autoregulatory system, as well as methods of enhancing or decreasing the expression of desired genes, and kits for carrying out these methods are described. The system was demonstrated in NIH3T3 cells and in \*\*\*transgenic\*\*\* mice. In the \*\*\*transgenic\*\*\* mice, inducibility, reversibility of the inducibility, and transmission of the \*\*\*transgenes\*\*\* from founders to progeny was shown.

L4 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 1996:746323 CAPLUS  
DN 126:15526

TI Glucose-responsive, insulin-producing \*\*\*transgenic\*\*\* pancreatic .beta.-cells with proliferation regulated by tetracycline

IN Elfrat, Shimon

PA Albert Einstein College of Medicine of Yeshiva University, USA

SO PCT Int. Appl., 33 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN,CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| PI | WO 9631242 | A1 | 19961010 | WO 1996-US4792 | 19960403 |
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| W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN |  |  |  |  |  |
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| CA 2217652 | AA | 19961010 | CA 1996-2217652 | 19960403 |  |
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| AU 9655375 | A1 | 19961023 | AU 1996-55375 | 19960403 |  |
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| AU 720662 | B2 | 20000608 |  |  |  |
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| EP 822834 | A1 | 19980211 | EP 1996-912816 | 19960403 |  |
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| JP 11505411 | T2 | 19990521 | JP 1996-530530 | 19960403 |  |
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| US 6114599 | A | 20000905 | US 1998-44297 | 19980319 |  |
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| US 6242254 | B1 | 20010605 | US 2000-492905 | 20000127 |  |
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| PRAI US 1995-418416 | A | 19950407 |  |  |  |
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| WO 1996-US4792 | W | 19960403 |  |  |  |
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| US 1998-44297 | A1 | 19980319 |  |  |  |
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AB Glucose-regulated insulin producing pancreatic .beta.-cells whose proliferation is controlled by tetracyclines are described for use in the treatment of diabetes. Proliferation is controlled by a fusion protein of the tetracycline repressor tetR and VP16 to regulate expression of an SV40 T antigen gene under control of a \*\*\*tet\*\*\* operator. The gene for the fusion protein is under control an insulin-responsive promoter. An animal carrying both constructs is prep. by crossing animals transformed with one of the constructs and .beta.-cells carrying the both constructs are selected in vitro. The construction of these cells in mice is demonstrated.

L4 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 1997:51843 CAPLUS  
DN 126:100260

TI Fusion proteins of the tetracycline repressor for use in tetracycline regulation of gene expression in eukaryotes

IN Bujard, Hermann; Gossen, Manfred; Hillen, Wolfgang; Helbl, Vera; Schnappinger, Dirk

PA BASF A.-G., Germany; Knoll Aktiengesellschaft

SO U.S., 62 pp., Cont.-in-part of U.S. Ser. No. 383,754.

CODEN: USXXAM

DT Patent

LA English

FAN,CNT 12

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| PI | US 5589362 | A | 19961231 | US 1995-485971 | 19950607 |
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| US 5464758 | A | 19951107 | US 1993-76726 | 19930614 |  |
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| US 5650298 | A | 19970722 | US 1994-260452 | 19940614 |  |
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| US 5654168 | A | 19970805 | US 1994-275876 | 19940715 |  |
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| US 5789156 | A | 19980804 | US 1995-383754 | 19950203 |  |
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| WO 9640892 | A1 | 19961219 | WO 1996-US9049 | 19960606 |  |
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| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE |  |  |  |  |  |
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| PRAI US 1993-76327 | B2 | 19930614 |  |  |  |
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| US 1993-76726 | A2 | 19930614 |  |  |  |
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| US 1994-260452 | A2 | 19940614 |  |  |  |
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| US 1994-270637 | B2 | 19940701 |  |  |  |
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| US 1994-275876 | A2 | 19940715 |  |  |  |
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| US 1995-383754 | A2 | 19950203 |  |  |  |
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| US 1995-485971 | A | 19950607 |  |  |  |
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AB Fusion proteins of amino acid-substituted \*\*\*tet\*\*\* repressors and transcription factors that bind class B \*\*\*tet\*\*\* operators that can be used in tetracycline regulation of expression of foreign genes in eukaryotes. Genes encoding these proteins are also described. The \*\*\*tet\*\*\* operators also have nucleotide substitutions in one or two of the 3'-bases (+4 or +6). A pool of multiply mutant \*\*\*tet\*\*\* repressor genes was generated by bisulfite mutagenesis of the tetR gene and mutants with a reverse regulation phenotype (induction of gene expression by tetracyclines rather than repression) were identified using a galK/lacZ/ \*\*\*tet\*\*\* operator reporter system. Fusion proteins of the N-terminal regions of these proteins and herpes simplex VP16 were prep. by std. methods. Their efficacy was tested in a reporter gene system using the CMV promoter and a heptameric \*\*\*tet\*\*\* operator to regulate expression of a luciferase reporter in HR-5 cells. Doxycycline induced gene expression by 237-1660-fold and two genes under the control of \*\*\*tet\*\*\* operators could be induced coordinately. Fusion proteins of silencer domains, e.g. Krueppel or v-erbA proteins, are described for use as repressors. A combinatorial anal. of amino acid-substituted analogs of the repressor and base-substituted analogs of the operator was undertaken to find combinations showing the most effective induction or repression.

L4 ANSWER 18 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS  
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AN 1996:316328 BIOSIS

DN PREV199699038684

TI Rapid retroviral delivery of tetracycline-inducible genes in a single autoregulatory cassette.

AU Hofmann, Andreas; Nolan, Garry P.; Blau, Helen M. (1)

CS (1) Dep. Mol. Pharmacol., Stanford Univ. Sch. Med., Stanford, CA 94305-5332 USA

SO Proceedings of the National Academy of Sciences of the United States of America, (1996) Vol. 93, No. 11, pp. 5185-5190.

ISSN: 0027-8424.

DT Article

LA English

AB We describe a single autoregulatory cassette that allows reversible induction of \*\*\*transgene\*\*\* expression in response to tetracycline (\*\*\*tet\*\*\*). This cassette contains all of the necessary components previously described by others on two separate plasmids that are introduced sequentially over a period of months (Gossen, M. & Bujard, H. (1992) Proc. Natl. Acad. Sci. USA 89, 5547-5551). The cassette is introduced using a retrovirus, allowing transfer into cell types that are difficult to transfect. Thus, populations of thousands of cells, rather than a few clones, can be isolated and characterized within weeks. To avoid potential interference of the strong retroviral long terminal repeat enhancer and promoter elements with the function of the \*\*\*tet\*\*\*-regulated cytomegalovirus minimal promoter, the vector is self-inactivating, eliminating transcription from the long terminal repeat after infection of target cells. Tandem \*\*\*tet\*\*\* operator sequences and the cytomegalovirus minimal promoter drive expression of a bicistronic mRNA, leading to transcription of the gene of interest (lacZ) and the internal ribosome entry site controlled transactivator (\*\*\*Tet\*\*\* repressor-\*\*\*VP16\*\*\* fusion\*\*\* protein). In the absence of \*\*\*tet\*\*\*, there is a progressive increase in transactivator by means of an autoregulatory loop, whereas in the presence of \*\*\*tet\*\*\*, gene expression is prevented. Northern blot, biochemical, and single cell analyses have all shown that the construct yields low basal levels of gene expression and induction of one to two orders of magnitude. Thus, the current cassette of the retroviral construct (SIN-RetroTet vector) allows rapid delivery of inducible genes and should have broad applications to cultured cells, \*\*\*transgenic\*\*\* animals, and gene therapy.

L4 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2003 ACS

AN 1996:622324 CAPLUS

DN 125:266875

TI Temporal control of the Cre recombinase in \*\*\*transgenic\*\*\* mice by a tetracycline responsive promoter

AU St-Onge, Luc; Furth, Priscilla A.; Gruss, Peter

CS Dep. Molecular Cell Bio., Max-Planck-Inst. Biophys. Chem., Goettingen, 37018, Germany

SO Nucleic Acids Research (1998), 24(19), 3875-3877

CODEN: NARHAD; ISSN: 0305-1048

PB Oxford University Press

DT Journal

LA English

AB Gene-targeted mice derived from embryonic stem cells are a useful tool to study gene function during development. However, if the mutation is embryonic lethal and the gene is deleted from the onset of development, later functions in adult animals cannot be studied. Recently, the bacterial Cre-loxP site-specific recombination system has successfully been used in \*\*\*transgenic\*\*\* animals to produce tissue-specific and temporal deletions [Tu et al. (1993) Cell, 73, 1155-1164; Gu et al. (1994) Science, 265, 103-106; Kuehn et al. (1995) Science, 269, 14237-1429]. We have evaluated the tetracycline responsive binary system [Gossen and Bujard (1992) Proc. Natl. Acad. Sci. USA, 89, 5547-5551] for its ability to transiently express the Cre recombinase in \*\*\*transgenic\*\*\* mice. In this system, a transactivator fusion protein composed of the tetracycline repressor (tetR) and the acidic domain of the herpes simplex viral protein 16 (VP16) can regulate the expression of the Cre gene from a promoter contg. \*\*\*tet\*\*\*-operator (tetO) sequences. In the absence of tetracycline, the Cre gene is expressed and will induce site-specific recombination between two loxP sites. In the presence of tetracycline, the Cre gene will not be expressed and recombination will not occur.

L4 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2003 ACS

AN 1995:510528 CAPLUS

DN 122:262575

TI Conditional transformation of a pancreatic .beta.-cell line derived from \*\*\*transgenic\*\*\* mice expressing a tetracycline-regulated oncogene

AU Efrat, Shimon; Fusco-DeMane, David; Lemberg, Hadas; Emran, Obaidullah A;

Wang, Xiaorong

CS Dep. of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY, 10461, USA

SO Proceedings of the National Academy of Sciences of the United States of America (1995), 92(8), 3578-80

CODEN: PNASA6; ISSN: 0027-8424

PB National Academy of Sciences

DT Journal

LA English

AB Conditional oncogene expression in \*\*\*transgenic\*\*\* mice is of interest for studying the oncoprotein requirements during tumorigenesis and for deriving cell lines that can be induced to undergo growth arrest and enhance their differentiated functions. We utilized the bacterial tetracycline (\*\*\*Tet\*\*\*)-resistance operon regulatory system (\*\*\*tet\*\*\* ) from Tn10 of Escherichia coli to control simian virus 40 (SV40) large tumor (T) antigen (TAg) gene expression and to generate

conditionally transformed pancreatic .beta. cells in \*\*\*transgenic\*\*\* mice. A fusion protein contg. the \*\*\*tet\*\*\* repressor (tetR) and the activating domain of the herpes simplex virus protein VP16, which converts the repressor into a transcription activator, was produced in .beta. cells of \*\*\*transgenic\*\*\* mice under control of the insulin promoter. In a sep. lineage of \*\*\*transgenic\*\*\* mice, the TAg gene was introduced under control of a tandem array of \*\*\*tet\*\*\* operator sequences and a minimal promoter, which by itself is not sufficient for gene expression. Mice from the two lineages were then crossed to generate double-\*\*\*transgenic\*\*\* mice. Expression of the tetR fusion protein in .beta. cells activated TAg transcription, resulting in the development of .beta.-cell tumors. Tumors arising in the absence of \*\*\*Tet\*\*\* were cultured to derive a stable .beta.-cell line. Cell incubation in the presence of \*\*\*Tet\*\*\* led to inhibition of proliferation, as shown by decreased BrdUrd and [3H]thymidine incorporation. The \*\*\*Tet\*\*\* deriv. anhydrotetracycline showed a 100-fold stronger inhibition compared with \*\*\*Tet\*\*\*. When administered in vivo, \*\*\*Tet\*\*\* efficiently inhibited .beta.-cell proliferation. These findings indicate that transformed .beta. cells selected for growth during a tumorigenesis process in vivo maintain a dependence on the continuous presence of the TAg oncoprotein for their proliferation. This system provides an approach for generation of .beta.-cell lines for cell therapy of diabetes as well as conditionally transformed cell lines from other cell types of interest.

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COST IN U.S. DOLLARS SINCE FILE TOTAL

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| FULL ESTIMATED COST | 73.78   | 73.99 |

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE TOTAL

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